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ECHOCARDIOGRAPHIC ABNORMALITIES IN THE METABOLIC SYNDROME

Dissertation submitted for DM
(Branch II – Cardiology)

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CERTIFICATE

This is to certify that this dissertation entitled **"Echocardiographic Abnormalities in the Metabolic Syndrome"** submitted by **Dr. G.S.Sivakumar** to The Tamil Nadu Dr. M. G. R. Medical University, Chennai is in partial fulfilment of the requirement for the award of DM Cardiology and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I, **Dr.G.S.Sivakumar** solemnly declare that I carried out this work on Echocardiographic Abnormalities in the Metabolic Syndrome at Department of Cardiology, Government Rajaji Hospital during the period of April 2007 – May 2009.

I also declare this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the DM Cardiology Degree examination.

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CONTENTS

INTRODUCTION

The metabolic syndrome is a collection of frequently associated cardiovascular risk factors that tend to aggregate in selected patient populations and that, together, increase coronary and cardiovascular mortality, and total mortality. The World Health Organization, has used this term to indicate a state of insulin resistance with pervasive dysmetabolism secondary to the state of insulin resistance. Conceptualization of the metabolic syndrome as a unique, high risk cardiovascular state, as defined by the National Cholesterol Education Program (NCEP), is gaining acceptance as the basis for diagnosing the metabolic syndrome. BMI remains an independent correlate of cardiac function, even after adjusting for age, mean arterial pressure, LV mass index, and insulin. Previous smaller studies have focused on conventional methods such as LVEF and fractional shortening, which are relatively insensitive and thus unable to detect early preclinical changes. The more sensitive, newer echo techniques have been used to demonstrate the presence of subclinical LV changes in young obese patients in recent studies. These functional changes are matched by changes in LV morphology.

REVIEW OF LITERATURE

The metabolic syndrome represents a clustering of cardiovascular risk factors affecting around 22% of the adult population in industrialized countries and over 40% of the those aged 50 and older. These risk factors have been shown to act synergistically, via mechanisms poorly defined, to increase the risk of adverse cardiovascular events including coronary artery disease (CAD) and congestive heart failure, and are associated with high cardiovascular morbidity and mortality.[1]

In 1988, Reaven first introduced the concept that insulin resistance clusters with glucose intolerance, dyslipidemia, and hypertension to increase cardiovascular risk [Reaven, 1988]. These abnormalities were related to insulin resistance (IR) by cause-effect relationships and it was emphasized that IR alone is insufficient to alter glucose tolerance. IR and hyperinsulinemia are neither strictly necessary nor sufficient to alter lipid metabolism, blood pressure, or vascular function. Each of these systems is under multifactorial control, and defects in one or more steps of its effector pathway are necessary to drive the system out of balance [Ferrannini, 2007]. In the 1990s, the so-called insulin resistance syndrome transmuted into the clinical metabolic syndrome (MetS), which has now taken hold in the medical literature.It represents a global public health problem. Since 1988, when Reaven first systematically described it, an abundance of research has advanced an understanding of the pathophysiology, epidemiology, prognostic implications, and therapeutic strategies related to the Metabolic syndrome.

Reaven's first definition of the Metabolic syndrome included these components: hyperglycemia, abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol concentration, and hypertension. Its pathogenesis, unified by the putative mechanism of insulin resistance, was thought to be related to interactions between sedentary lifestyle, diet, and genetic factors. In 1998, the American Diabetes Association proposed that Metabolic syndrome is comprised of glucose intolerance, central obesity, dyslipidemia (including increased triglycerides, decreased high-density lipoprotein cholesterol concentration, and increased small dense low density lipoprotein cholesterol concentration), hypertension, increased prothrombotic and antifibrinolytic factors, and risk for atherosclerotic disease[2]; In 1999, the World Health Organization (WHO) codified specific components and thresholds for the Metabolic syndrome, and in 2003 the U.S. National Cholesterol Education Program (NCEP) redefined the Metabolic syndrome in an attempt to simplify the clinical application of its criteria and improve its recognition. Despite these efforts, there exists no genuine consensus of the unique components that comprise the Metabolic Syndrome[3].

Clinical Diagnosis of the Metabolic Syndrome

Several different sets of criteria have been proposed during the past decade for diagnosis of the metabolic syndrome. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed a simple set of diagnostic criteria based on common clinical measures including waist circumference, triglycerides, HDL-C, blood pressure, and fasting glucose level. The presence of defined

abnormalities in any 3 of these 5 measures constitutes a diagnosis of the metabolic syndrome[1]. The ATP III criteria for the metabolic syndrome have been widely used in both clinical practice and epidemiological studies. The criteria also have the advantage of avoiding emphasis on a single cause. In the absence of compelling scientific reasons for change, the AHA and NHLBI affirm the overall utility and validity of the ATP III criteria and propose that they continue to be used with minor modifications and clarifications.

These modifications and clarifications include allowing for adjustment of waist circumference to lower thresholds when individuals or ethnic groups are prone to insulin resistance; allowing triglycerides, HDL-C levels, and blood pressure to be counted as abnormal when a person is taking drug treatment for these factors; clarifying that the definition of elevated blood pressure is a level that exceeds the threshold for either systolic or diastolic pressure; and reducing the threshold for counting elevated fasting glucose from >110 mg/dL to >100 mg/dL, in accordance with the American Diabetes Association's (ADA's) revised definition of impaired fasting glucose (IFG). Recently, the International Diabetes Federation (IDF) has proposed a set of clinical criteria that are similar to those of the updated ATP III criteria. In fact, thresholds are identical for triglycerides, HDL-C, blood pressure, and plasma glucose. The updated AHA/NHLBI diagnostic criteria maintain ATP III waist circumference thresholds for Americans, except that a lower threshold can be invoked for individuals who are especially prone to insulin resistance, particularly Asian Americans. Abdominal obesity is highly correlated

with and easier to measure than other indicators of insulin resistance. The IDF therefore concluded that abdominal obesity incorporates both concepts of obesity and insulin resistance as being the 2 major underlying risk factors of the metabolic syndrome[4]; thus, they made increased waist circumference a required element for diagnosing the metabolic syndrome. In the updated ATP III classification, increased waist circumference is not deemed a necessity if 3 other risk factor criteria are present. Despite these minor differences in criteria for diagnosis, in the US population, updated ATP III and IDF criteria identify essentially the same individuals as having the metabolic syndrome[5].

Features of the metabolic syndrome as defined according to the Adult Treatment Panel III of the National Cholesterol Education Program (ATPIII-NCEP) are:

1. Waist circumference > 102 cm in men and > 88 cm in women;
2. Fasting serum triglycerides ≥ 150 mg/dl;
3. High-density lipoprotein (HDL) cholesterol < 40 mg/dl in men and < 50 mg/dl in women;
4. High blood pressure: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or antihypertensive drug treatment;
5. High glucose levels: fasting serum glucose ≥ 110 mg/dl or clinical diagnosis of diabetes.

The World Health Organisation's clinical criteria for the metabolic syndrome.

Insulin resistance, identified by one of the following:

- Type 2 diabetes mellitus
- Impaired fasting glucose
- Impaired glucose tolerance
- Or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinaemic, euglycaemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140/90 mm Hg)
- Plasma triglycerides ≥150 mg/dL
- HDL-C <35 mg/dL in men or <39 mg/dL in women
- Body mass index >30 kg/m^2 and/or waist to hip ratio >0.9 in men and > 0.85 in women
- Urinary albumin excretion rate ≥20 microgram /min or albumin:creatinine ratio ≥30 mg/g.

The International Diabetes Federation's definition of the metabolic syndrome.

Central obesity (defined as waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity specific values for other groups*)

Plus any 2 of the following 4 factors:

- Raised triglyceride level ≥150 mg/dL, or specific treatment for this lipid abnormality

- Reduced HDL-C <40 mg/dL in males, <50 mg/dL in females, or specific treatment for this lipid abnormality
- Raised BP: systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose ≥100 mg/dL, or previously diagnosed type 2 diabetes

*South Asians and Chinese: ≥90 cm for males, ≥80 cm for females.

Japanese: ≥85 cm for males, ≥90 cm for females.

Ethnic South and Central Americans: Use South Asian recommendations until more specific data are available.

East Mediterranean, Middle East (Arab) and sub-Saharan populations: Use European data until more specific data are available.

Modified ATP-III-1 [MS1]: WC cutoffs ≥90 cm for men and ≥80 cm for women. Criteria from 2 to 5 were unchanged as per the NCEP ATP-III description above.

Modified ATP-III-2 [MS2]: BMI cutoff at ≥23 Kg/m2 in addition to the criteria used in MS1.

Modified WHO [MS3]: The definitions were same as for the WHO criteria except for WHR of ≥0.89 in males and ≥0.81 in females and a BMI ≥23 kg/m.

Distinct clinical features and metabolic predispositions are frequently noted in people with abdominal adiposity, insulin resistance, dyslipidemia, and HTN. To simplify the recognition of such a clustering, the WHO laid down definitive criteria

(WHO 1999), followed by the MS definition of NCEP–ATP-III (ATP-III 2001) and IDF (Albert et al 2005). The Center for Disease Control and Prevention and US Department of Health and Human Services have attributed a specific code to "dysmetabolic syndrome" (ICD #277.7) (CDC 2002) in the 9th revision in clinical classification, thus bestowing it with an implicative dignity.

Clinical criteria of the American Association of Clinical Endocrinologists for diagnosis of the Insulin Resistance Syndrome

Diagnosis depends on clinical judgement based on risk factors.

Risk factor components	Cut-off points for abnormality
Overweight/obesity	Body mass index ≥25 kg/mÇ
Elevated triglycerides	≥150 mg/dL
Low HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Elevated blood pressure	≥130/85 mm Hg
2-hour post-glucose challenge	>140 mg/dL
Fasting glucose	110-126 mg/dL
Other risk factors	Family history of type 2 diabetes mellitus, hypertension, or cardiovascular disease
	Polycystic ovary syndrome
	Sedentary lifestyle
	Advancing age
	Ethnic groups having high risk for 2 diabetes mellitus or cardiovascular disease

Epidemiology of the Metabolic syndrome:

Reviewing the literature for studies investigating the epidemiology of the MetS

reveals limited and conflicting data. Asian Indians are a high-risk population with respect to diabetes mellitus and CVD and the numbers are consistently on the rise (Enas et al 1992; Enas and Senthilkumar 2001). It has long been doubted that the above standard definitions of MS under- represents its prevalence in the Asian Indian community, thereby delaying the commencement of definite preventive and therapeutic efforts in many individuals. The results of various studies have appreciated ethnic variation in clinical measures and disease outcomes in different populations (Anand et al 2003; Tan et al 2004).

Part of the problem lies in the cutoffs for obesity as defined by the WHO and ATP-III, which are not valid for Asian Indians. This population is of smaller build, has high insulin resistance and a dysmetabolic adipocyte milieu at considerably lower BMI and abdominal adiposity as identified by a large WC (Cooppan 2005). In the wake of ongoing debate and a lack of consensus, the WHO recognized the need for population specifi c cutoff definitions in order to make the diagnosis of MS more precise and modified the BMI cutoff in Asians (WHO 2004). Also, the IDF (Albert et al 2005) published consensus cutoff for WC that are more ethnic-specific, based on the Chinese, Malay, and Asian Indian populations. In one study, three candidate definitions were revised for MS by substituting the above modified cutoffs for BMI and WC, as also the WHR in the ATP-III and WHO definitions while IDF criteria was independently assessed in this study. A consistent gain in MS diagnosis was achieved by applying the modified definitions over the standard ones. Maximum gain was obtained in the MS2

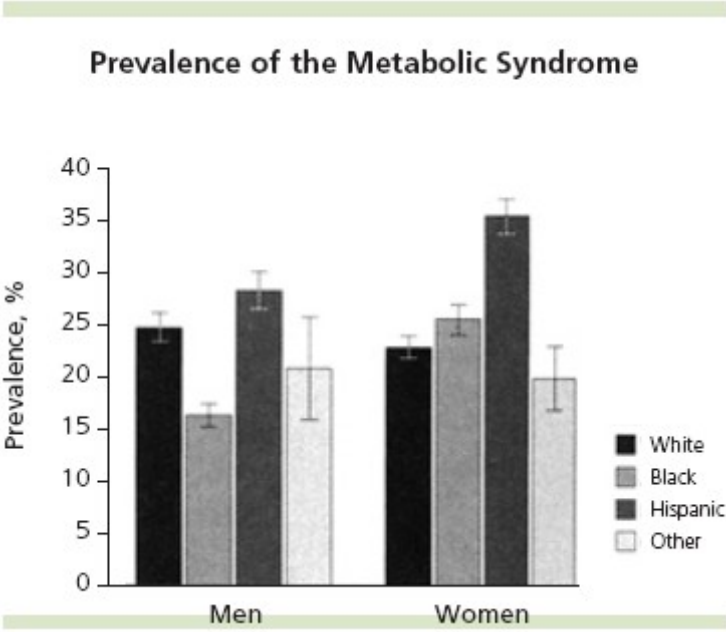
group as defined by applying modified WC and BMI over and above the MS1 definition, which used only a modification in WC in its criteria. A comparable finding was reported using modified ATP-III criteria for anthropometry, which included skin fold thickness measurements in their candidate definition (Misra et al 2005). The IDF proposed that central obesity is an essential component of MS, while the American Heart Association/National Heart,

Lung and Blood Institute (AHA/NHLBI) opines that it is an optional component similar to the other MS factors. Also, the IDF supported a modified cut off in impaired fasting glucose (IFG) levels ≥ 100 mg/dL as compared with ≥110 mg/dL set by other criteria. The various definitions were applied to a cohort with high risk for CAD where all participants had a family history of premature onset of CAD[7]. MS prevalence was higher in that cohort in comparison to other studies. At baseline, ATP-III labeled a significantly higher proportion of people with MS when compared with the WHO criteria. Distribution of MS across various age groups showed a gradual increase in prevalence with advancing age in both males and females in that cohort with maximum prevalence in the 50–59 age group. Distribution of MS prevalence was similar across age groups in MS1, MS2, and IDF categories. Tan and colleagues (2004) reported a similar trend in prevalence.

In this context, early detection of MS would be of immense importance to deploy prophylactic measures against component risk factors of MS. The modified ATP-III criteria [MS1 and MS2] were able to identify greater number of young people with MS

[30–39 yrs] than the WHO criteria. Hence the above modifications do indicate their ability to identify the 'high-risk subjects' much earlier.

The NCEP definition is more flexible as it can diagnose MS even in the absence of glucose intolerance, which in itself is a predisposition to dysmetabolic dyslipidemia, an obesity phenotype and a pro-inflammatory status. The WHO criteria, on the other hand, mandate the presence of diabetes with the inclusion of microalbuminuria, which is not only a marker for renal disease, but also for CVD. By the time most patients receive a diagnosis of diabetes, they are more than likely to have developed micro- or macro-vascular disease (Enas et al 1992). It can thus be expected that a greater proportion of the patients will have CVD, if MS is determined based on the WHO guidelines. Employing the MS2 and MS3 criteria, those with MS but without CVD were identified .Subjects with MS were on an average ten years older than those without the syndrome. Significantly larger number of people with MS were hypertensive and diabetic with higher anthropometric parameters and incidence of CVD when compared with those without MS[8]. BMI showed correlation with WC but not with WHR, which indicates that WC and BMI may be better predictors of MS when compared with WHR in Asian Indians. Kurpad and colleagues (2003) found similar correlation between WC and BMI and suggest that WC is a better marker of abdominal obesity than WHR.



Age-adjusted prevalence of the metabolic syndrome among 8,814 U.S. adults at least 20 years of age, by sex and race or ethnicity, from the National Health and Nutrition Examination Survey III, 1988-1994[6].

Components of Metabolic Syndrome

ATP III1 identified 6 components of the metabolic syndrome that relate to CVD[9,10,11]:

- Abdominal obesity (↑ waist circumference)
- Atherogenic dyslipidaemia (↑ triglycerides, ↓ HDL-C, ↑ ApoB, ↑ small LDL particles)
- Elevated blood pressure
- Insulin resistance ± glucose intolerance (IFG and/or IGT)
- Proinflammatory state (↑ hsCRP)
- Prothrombotic state (↑ PAI-1, ↑ FIB)

- Other features: endothelial dysfunction, microalbuminuria, polycystic ovary syndrome, hypoandrogenism, non-alcoholic fatty liver disease, hyperuricaemia, and disturbances of the phosphate and magnesium metabolism

Clinical syndromes associated with the metabolic syndrome.[9,10]

1. Type 2 diabetes mellitus
2. Cardiovascular disease
3. Essential hypertension
4. Polycystic ovary syndrome
5. Non-alcoholic fatty liver disease
6. Certain forms of cancer
7. Sleep apnoea

These components of the metabolic syndrome constitute a particular combination of what ATP III terms underlying, major, and emerging risk factors. According to ATP III, underlying risk factors for CVD are obesity (especially abdominal obesity), physical inactivity, and atherogenic diet; the major risk factors are cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, family history of premature coronary heart disease (CHD), and aging; and the emerging risk factors include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, proinflammatory state, and prothrombotic state. For present purposes, the latter 5 components are designated metabolic risk factors. Each component of the

metabolic syndrome will be briefly defined.

- Abdominal obesity is the form of obesity most strongly associated with the metabolic syndrome. It presents clinically as increased waist circumference.
- Atherogenic dyslipidemia manifests in routine lipoprotein analysis by raised triglycerides and low concentrations of HDL cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities, eg, increased remnant lipoproteins, elevated apolipoprotein B, small LDL particles, and small HDL particles. All of these abnormalities have been implicated as being independently atherogenic.
- Elevated blood pressure strongly associates with obesity and commonly occurs in insulin-resistant persons. Hypertension thus commonly is listed among metabolic risk factors. However, some investigators believe that hypertension is less "metabolic" than other metabolic-syndrome components. Certainly, hypertension is multifactorial in origin
- Insulin resistance is present in the majority of people with the metabolic syndrome. It strongly associates with other metabolic risk factors and correlates univariately with CVD risk[5]. These associations, combined with belief in its priority, account for the term insulin resistance syndrome. Even so, mechanisms underlying the link to CVD risk factors are uncertain, hence the ATP III's classification of insulin resistance as an emerging risk factor. Patients with longstanding insulin resistance frequently manifest glucose intolerance, another

emerging risk factor. When glucose intolerance evolves into diabetes-level hyperglycemia, elevated glucose constitutes a major, independent risk factor for CVD.

- A proinflammatory state, recognized clinically by elevations of C-reactive protein (CRP), is commonly present in persons with metabolic syndrome. Multiple mechanisms seemingly underlie elevations of CRP. One cause is obesity, because excess adipose tissue releases inflammatory cytokines that may elicit higher CRP levels.
- A prothrombotic state, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the metabolic syndrome. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected.

Pathogenesis of Metabolic Syndrome

The metabolic syndrome seems to have 3 potential etiological categories: obesity and disorders of adipose tissue; insulin resistance; and a constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the metabolic syndrome. Other factors—aging, proinflammatory state, and hormonal changes—have been implicated as contributors as well.

Obesity and Abnormal Body Fat Distribution

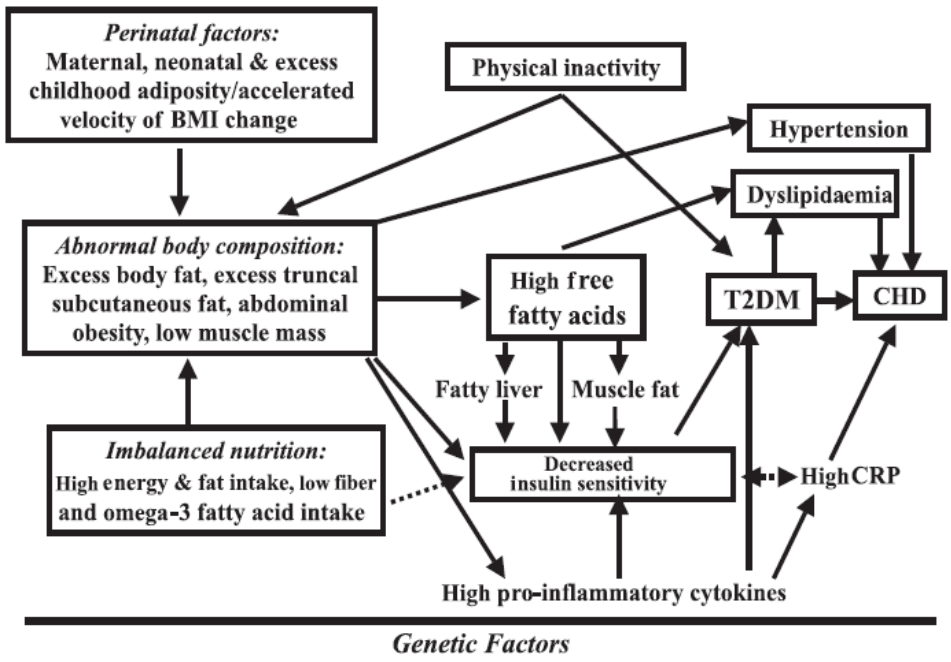
ATP III considered the "obesity epidemic" as mainly responsible for the rising prevalence of metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL cholesterol, and hyperglycemia, and it otherwise associates with higher CVD risk. Abdominal obesity especially correlates with metabolic risk factors. Excess adipose tissue releases several products that apparently exacerbate these risk factors. They include nonesterified fatty acids (NEFA), cytokines, PAI-1, and adiponectin. A high plasma NEFA level overloads muscle and liver with lipid, which enhances insulin resistance. High CRP levels accompanying obesity may signify cytokine excess and a proinflammatory state. An elevated PAI-1 contributes to a prothrombotic state, whereas low adiponectin levels that accompany obesity correlate with worsening of metabolic risk factors. The strong connection between obesity (especially abdominal obesity) and risk factors led ATP III to define the metabolic syndrome essentially as a clustering of metabolic complications of obesity.

Insulin Resistance

A second category of causation is insulin resistance. Many investigators place a greater priority on insulin resistance than on obesity in pathogenesis. They argue that insulin resistance, or its accomplice, hyperinsulinemia, directly causes other metabolic risk factors. Identifying a unique role for insulin resistance is complicated by the fact

that it is linked to obesity. Insulin resistance generally rises with increasing body fat content, yet a broad range of insulin sensitivities exists at any given level of body fat.4 Most people with categorical obesity (body mass index [BMI] ≥ 30 kg/m2) have postprandial hyperinsulinemia and relatively low insulin sensitivity, 5 but variation in insulin sensitivities exists even within the obese population.4 Overweight persons (BMI ≥ 25 to 29.9 kg/m2) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance. In some populations (eg, South Asians), insulin resistance occurs commonly even with BMI _25 kg/m2 and apparently contributes to a high prevalence of type 2 diabetes and premature CVD. South Asians and others who manifest insulin resistance with only mild-to-moderate overweight can be said to have primary insulin resistance. Even with primary insulin resistance, however, weight gain seems to enhance insulin resistance and metabolic syndrome. Thus, dissociation of obesity and primary insulin resistance in patients with metabolic syndrome is difficult. This is not to say that insulin resistance per se does not play a significant role in causation of metabolic syndrome. When insulin-resistant muscle is already overloaded with lipid from high plasma NEFA levels, some excess NEFA presumably is diverted to the liver, promoting fatty liver and atherogenic dyslipidemia. Hyperinsulinemia may enhance output of very low- density lipoprotein triglycerides, raising triglycerides. Insulin resistance in muscle predisposes to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver. Finally, insulin resistance may raise blood pressure by a variety of mechanisms.

Complex interactions of genetic, perinatal, nutritional and other acquired factors in development of insulin resistance, type 2 diabetes and coronary heart disease in South Asians are shown below:



Independent Factors That Mediate Specific Components of the Metabolic Syndrome

Beyond obesity and insulin resistance, each risk factor of the metabolic syndrome is subject to its own regulation through both genetic and acquired factors. This leads to variability in expression of risk factors. Lipoprotein metabolism, for instance, is richly modulated by genetic variation; hence, expression of dyslipidemias in response to obesity and/or insulin resistance varies considerably. The same holds for blood pressure regulation. Moreover, glucose levels depend on insulin-secretory capacity as well as insulin sensitivity. This variation in distal regulation cannot be ignored as an important

factor in causation of metabolic syndrome.

Other Contributing Factors

Advancing age probably affects all levels of pathogenesis, which likely explains why prevalence of the metabolic syndrome rises with advancing age. Recently, a proinflammatory state has been implicated directly in causation of insulin resistance, as well as atherogenesis. Finally, several endocrine factors have been linked to abnormalities in body-fat distribution and hence indirectly to metabolic syndrome. Thus, pathogenesis of the metabolic syndrome is complex and ripe with opportunities for further research.

Issue of Oral Glucose Tolerance Test

Both WHO and AACE include IGT, detected by oral glucose tolerance test (OGTT) or 2-hour postglucose challenge, among the risk factors for metabolic syndrome. ATP III did not include it because of the added inconvenience and cost of OGTT in clinical practice[9,10].

Therapeutic Implications Obesity and Body Fat Distribution as Targets of Therapy

ATP III recommended that obesity be the primary target of intervention for metabolic syndrome. First-line therapy should be weight reduction reinforced with increased physical activity. Weight loss lowers serum cholesterol and triglycerides, raises HDL cholesterol, lowers blood pressure and glucose, and reduces insulin resistance. Recent data further show that weight reduction can decrease serum levels of

CRP and PAI-1.

Insulin Resistance as Target of Therapy

If insulin resistance, whether primary or secondary to obesity, is in the chain of causation of metabolic syndrome, it would be an attractive target. Certainly, weight reduction and increased physical activity will reduce insulin resistance. Insulin resistance as a target has caught the imagination of the pharmaceutical industry, and drug discovery is underway. Two classes of drugs are currently available that reduce insulin resistance. These are metformin and insulin sensitizers such as thiazolidinediones (TZDs). Metformin has long been used for treatment of type 2 diabetes. In UKPDS, metformin apparently reduced new onset CHD in obese patients with diabetes[5,11]. In the Diabetes Prevention Program, metformin therapy prevented (or delayed) onset of type 2 diabetes in persons with IGT. There are, however, no CVD end-point studies on metformin treated patients with metabolic syndrome[12]. Thus, at present, metformin cannot be recommended for the express purpose of reducing risk for CVD in persons with the metabolic syndrome.

TZDs currently are approved for treatment of type 2 diabetes[15]. They reduce insulin resistance, favorably modify several metabolic risk factors, and reverse abnormal arterial responses. Nonetheless, no clinical trial data yet exist to document benefit in CVD risk reduction. Thus, in spite of promise, TZDs cannot be recommended at present for preventing CVD in patients with either metabolic syndrome or diabetes[10,12].

Specific Metabolic Risk Factors as Targets of Therapy

Atherogenic Dyslipidemia

Although statins typically are recognized to be LDL-lowering drugs, they reduce all apolipoprotein B–containing lipoproteins. Recent subgroup analyses of statin trials reveal that statins reduce risk for CVD events in patients with metabolic syndrome. Fibrates also favorably modify atherogenic dyslipidemia and may directly reduce atherogenesis. Post hoc analysis of recent fibrate trials strongly suggests that they reduce CVD end points in patients with atherogenic dyslipidemia and metabolic syndrome. Moreover, clinical studies demonstrate that abnormal lipoprotein patterns are doubly improved by combined statin-fibrate therapy, but just how much this combination reduces CVD events beyond statins alone awaits demonstration with controlled clinical trials.

Elevated Blood Pressure

There is full agreement that hypertensive patients with metabolic syndrome deserve lifestyle therapies to reduce blood pressure. In addition, antihypertensive drugs should be used as recommended by hypertension guidelines.

Prothrombotic State

No drugs are available that target PAI-1 and fibrinogen. An alternative approach to the prothrombotic state is antiplatelet therapy. For example, low-dose aspirin reduces CVD events in both secondary and primary prevention. Thus, use of aspirin for primary prevention in patients with metabolic syndrome is promising. According to current recommendations, low-dose aspirin therapy has a favorable efficacy/side effect ratio

when 10-year risk for CHD is > 10%.

Proinflammatory State

There is growing interest in development of drugs to dampen the proinflammatory state. Several lipid-lowering drugs will reduce CRP levels, which could reflect an anti-inflammatory action.

Hyperglycemia

When patients with metabolic syndrome develop type 2 diabetes, they are at high risk for CVD. All CVD risk factors should be intensively reduced. In addition, glucose levels should be appropriately treated with lifestyle therapies and hypoglycemic agents as needed to keep hemoglobin A1c levels below guideline targets.

Cardiac changes in structure and function in metabolic syndrome

LV Mass

Increased LV mass is associated with coronary heart disease, stroke, and heart failure. Metabolic syndrome has been associated with prevalent CVD in most studies, including the population-based Strong Heart Study[27].

This observation is of clinical importance because treatment leading to regression in LV mass can improve cardiovascular prognosis. In one study (Bilal Aizaz, 2008) women with metabolic syndrome had a greater LV mass index than women without metabolic syndrome, demonstrating that women with metabolic syndrome already manifest measurable abnormalities in LV structure[27]. In another study(Lisa de las Fuentes, 2006) although LV volumes and LVEF were similar among the three groups of

Absent metabolic syndrome, Pre-Metabolic syndrome and metabolic syndrome, RWT and LVM/Ht2 and the prevalence of diastolic dysfunction increased progressively from the Absent to the Pre-Metabolic Syndrome and Metabolic Syndrome groups[28]. Of note, the Absent group, while not meeting any criteria for metabolic syndrome, did not represent a 'normal control' group since 47% were either overweight or obese. This study revealed that while each of the variables contributing to metabolic syndrome was correlated with LV relaxation (i.e. Veglobal) in univariate analyses (HDL-C excluded), only diastolic blood pressure, waist circumference, and triglyceride remained independently associated with Veglobal in models that also included age and LV mass[28].

Echocardiography, performed at 1 of 4 sites in the Atherosclerosis Risk in Communities (ARIC) Study, was used to assess LV dimensions in 1572 black women and men aged 49 to 75 years in 1993–1996. Participants were categorized by number of metabolic syndrome characteristics (hypertension, dyslipidemia [low HDL cholesterol or high triglycerides], and glucose intolerance). Age-adjusted mean LV mass indexed by height (g/m^2) increased in a stepwise gradient with increasing number of metabolic syndrome disorders (none, any 1, any 2, all 3) in both women and men (125.1, 143.9, 153.7, 169.3 and 130.5, 148.7, 160.8, 170.2, respectively; $P<0.001$, tests for trend). Associations were diminished slightly by adjustment for smoking, alcohol intake, and education; additional adjustment for waist circumference resulted in some attenuation, but associations remained statistically significant. Analyses focusing on components of LV mass revealed that posterior wall and interventricular septal thickness, but not LV

chamber size, were significantly and independently associated in general with the number of metabolic syndrome disorders. Consistent with these findings, relative wall thickness was also associated with number of disorders. Associations were similar across age and central adiposity. Hypertension had a strong influence on LV mass with additional contributions from dyslipidemia and glucose intolerance; strong synergistic effects of the syndrome beyond its individual components were not observed. In another cross-sectional study of the general population by Ana Azevedo. Increasing severity of metabolic syndrome was associated with increasingly compromised structure and function of the heart. This association was independent of Framingham risk score for indirect indices of diastolic dysfunction but not systolic dysfunction, and was not explained by blood pressure level. Parameters of left ventricular geometry patterns, left atrial diameter and diastolic dysfunction maintained this trend when taking into account the 10-year predicted risk of coronary heart disease by the Framingham score as an independent variable, while left ventricular systolic dysfunction did not. The prevalence of left ventricular diastolic dysfunction, and the mean left ventricular mass, left ventricular diameter and left atrial diameter increased significantly with the number of features of the metabolic syndrome when additionally adjusting for systolic blood pressure as a continuous variable.

LV Diastolic dysfunction

In the study by Lisa de las Fuentes, 2006[28], measurements of diastolic (Ve)

function worsened progressively from the Absent to the Pre-Metabolic Syndrome and Metabolic Syndrome groups, indicating impairment in diastolic function with increasing burden of metabolic syndrome. Increased LV mass, RWT, and deceleration time have been reported in hypertensive subjects with metabolic syndrome compared with a hypertensive cohort without the syndrome. In the Strong Heart Study, those with metabolic syndrome had greater LV mass and RWT and significantly lower E/A ratio; however, LV diastolic function was not characterized in Pre-Metabolic Syndrome. This study, by use of improved measures to detect LV relaxation (i.e. Ve), identifies a Pre-Metabolic Syndrome group with impaired LV diastolic function. In 2 previous studies of patients with established hypertension, the prevalence of LV diastolic dysfunction in metabolic syndrome was slightly increased (defined by Doppler flow and tissue Doppler imaging) or no different (defined by transmitral E/A velocity ratio only).30,32 Because blood pressure and serum glucose level both positively correlated with LV mass index and LV diastolic dysfunction in the study by Bilal Aizaz, 2008 , the modest magnitude of the increase in LV diastolic dysfunction among persons with isolated metabolic syndrome was likely due to the exclusion of patients with diabetes mellitus and hypertension. When those patients were included in the analysis, a progression was seen in LV diastolic dysfunction from no metabolic syndrome to isolated metabolic syndrome to metabolic syndrome that included hypertension and diabetes. This progressive increase in LV mass index and LV diastolic dysfunction is consistent with the concept that isolated metabolic syndrome is an early stage in the evolution of a risk factor

complex, which is reflected in progressive adverse remodeling and LV diastolic dysfunction.

The association of LV diastolic dysfunction with metabolic syndrome in women was most strongly influenced by waist circumference and elevated blood pressure. Metabolic syndrome is characterized by insulin resistance, which is strongly associated with central obesity. Indeed, central obesity has been proposed to be an important underlying pathophysiologic factor in metabolic syndrome.

Echocardiographic techniques

Diastolic dysfunction was assessed by pulsed-wave Doppler examination of mitral flow (before and during Valsalva maneuver) and pulmonary venous inflow, as well as by Doppler tissue imaging of the mitral annulus. Diastolic dysfunction was graded on a 4-point ordinal scale: normal; mild diastolic dysfunction, defined as abnormal relaxation without increased LV end-diastolic filling pressure (peak early (E) to peak late [atrial] [A] diastolic filling velocity ratio <0.75); moderate or "pseudonormal" diastolic dysfunction, defined as abnormal relaxation with increased LV end-diastolic filling pressure (E/A ratio of 0.75 to 1.5, deceleration time >140 ms, and 2 other Doppler indices of elevated LV end-diastolic filling pressure); or severe diastolic dysfunction, defined as advanced reduction in compliance with restrictive filling (E/ A ratio >1.5, deceleration time <140 ms, and Doppler indices of elevated LV end-diastolic filling pressure).

Recent advances in the field of echocardiography have made it possible to

objectively quantify regional in addition to global myocardial function. Indeed, with the introduction of tissue deformation imaging echocardiographic techniques which include tissue Doppler imaging (TDI) and speckle tracking (ST) methods[13], the inherent problems with earlier echocardiographic techniques of uni-dimensional imaging and limitations with regards to regional ventricular wall abnormalities have largely been overcome.

With these techniques, fractional change in length of a part of the myocardium compared to its original length, or strain (ε) is possible and as strain reflects deformation of the myocardium, it directly describes the contraction/relaxation pattern. This technique also makes it possible to measure the strain rate (SR), which represents the rate of deformation. To optimally assess regional myocardial function, both strain and SR need to be calculated since they provide complementary information: end systolic strain estimates EF and peak systolic SR is a measure of contractility[13,14].

The deformation occurs in three dimensions, which are expressed along three ventricular coordinates: a longitudinal and circumferential shortening and a radial thickening. The deformation is calculated based on the relative change of the length of myocardial fibers during the cardiac cycle and is expressed in a one dimensional parameter termed strain (ε). The local end-systolic strain value reflects the regional ejection fraction (EF) and the global LV end-systolic strain reflects the LVEF[14].

The cardiac deformation can also be represented graphically: S-wave represents the negative deflection occurring during systole with the peak negative deflection

representing maximal longitudinal myocardial shortening (or peak systolic strain). With the start of diastole, the myocardial fibers start regaining their original length.

Graphically, it is represented in three phases: (1) the early or rapid filling phase (E-wave) followed by (2) a plateau phase or diastasis, and finally (3) atrial filling (A-wave). The speed at which the myocardial deformation occurs is the SR and is expressed in s-1. SR depicts the change in strain over a period of time.

Myocardial deformation imaging techniques

Tissue Doppler Imaging and Speckle Tracking methods using B mode images are the two ultrasound based techniques used for evaluating myocardial deformation[13,14].

Tissue Doppler Imaging

During longitudinal shortening of myocardium there is a gradual increase in velocity from the apex to a maximum velocity at annular plane. This change in velocity called velocity gradient is used to calculate the SR by measuring the difference in velocity of the distal (v1) and the proximal (v2) point within defined region of interest (ROI), and the distance (x) between these two points. The following formula is used to calculate the strain rate:

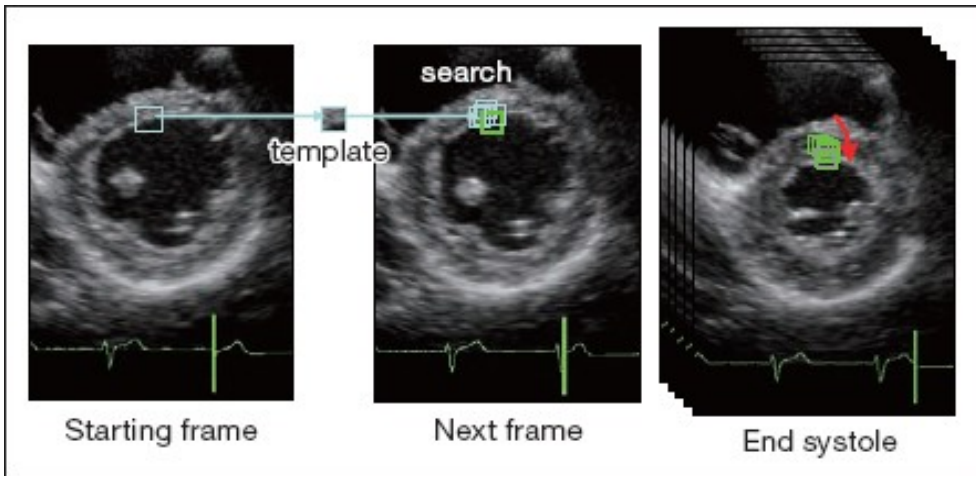
$$SR = \Delta v/\Delta x = v1 - v2/\Delta x.$$

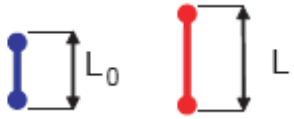
Strain is calculated from the SR values by temporal integration. Strain rate is, as opposed to strain alone, especially helpful in identifying infarcted tissue where the infracted segment does not deform during systole and there is no change in velocities.

The calculated SR would be zero in such case although the segment could show a displacement and velocity due to tethering of a functional neighboring segment.

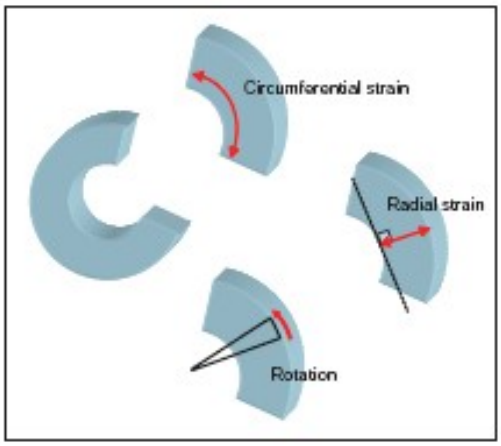
Wall Motion Tracking Technology

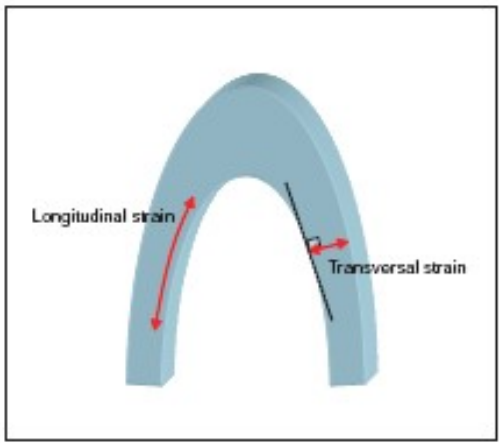
Two Dimensional Tracking (2DT) is an application of pattern matching technology to Ultrasound Cine data also commonly known as Speckle Tracking. A template image is created using a local myocardial region in the starting frame of the image data. In the next frame an algorithm searches for the local speckle pattern that most closely match the template. A movement vector is then created using the location of the template and the matching pattern in the subsequent frame. Multiple templates are used to observe movement of the entire myocardium. The process is then repeated by creating new templates and observing their movement in the subsequent frames until the entire cardiac cycle has been assessed. This method does not make use of Doppler information, so there is no Doppler angle dependency.

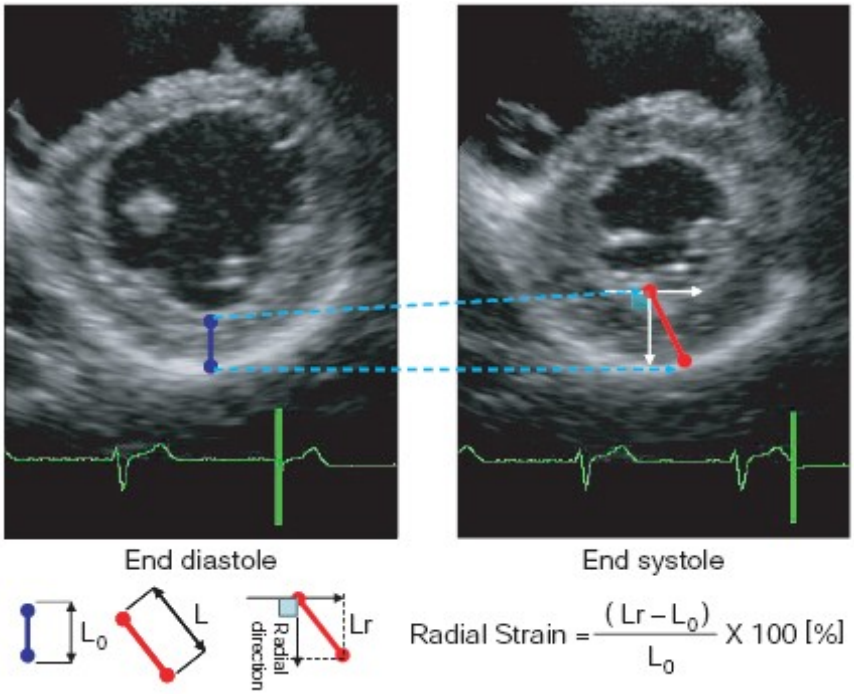




$$\text{Strain} = \frac{(L - L_0)}{L_0} \times 100\ [\%]$$







Comparison Between TDI and Speckle Tracking

Parameter	**TDI**	**Speckle tracking**
One-dimensional/bidimensional use	One dimensional	Bi-dimensional
SR variability by change in insonation angle	Marked	Minimal

Effect of artifacts like reverberations and side lobes	Marked	Minimal
Calculation of ventricular rotation and twist (additional parameters for LV function)	No	Yes
Influence of tachycardia on image acquisition	Not influenced	Undersampling
Training requirements	Difficult	Relatively easy
Post-processing time	Longer	Shorter
Reproducibility (for LV)	Lesser	Greater

Clinical Applications[13,14]

Tissue deformation imaging has given us recent new insights into ventricular function, adaptation, and mal-adaptation in response to pathology.

a. As mentioned previously, these techniques can be used to accurately and reproducibly measure global right and left ventricular function and regional wall deformation.
b. TDI is one of the most promising techniques for guiding patient selection for cardiac resynchronization therapy.
c. They can be used as robust techniques to determine diastolic dysfunction.
d. TDI has been shown to have a role in detecting cardiac ischemia and myocardial viability during stress echocardiography in patients with coronary artery disease and LV dysfunction. Doppler myocardial imaging is also a very sensitive marker of sub-endocardial dysfunction.
e. Measurement of myocardial velocities can discriminate between physiological

and pathological hypertrophy and can be used to monitor regression of LV hypertrophy under pharmacological treatment.

f. ST has been suggested to reliably distinguish between hypertrophic cardiomyopathy and hypertrophy associated with hypertension.

Metabolic Syndrome as a Risk Condition

It seems self-evident that a condition characterized by multiple risk factors will carry a greater risk for adverse clinical outcomes than will a single risk factor. This conclusion is implicit in Framingham risk equations, which incorporate many of the components of the metabolic syndrome. For this conference, Framingham investigators examined their extensive database for the relation between metabolic syndrome and future development of both CVD and diabetes. Their analysis was carried out on 3323 Framingham offspring men and women (mean age, 52 years) in 8 years of follow-up.

Metabolic Syndrome as a Predictor of CVD

Individuals with metabolic syndrome are at increased risk for CHD.10 In Framingham, the metabolic syndrome alone predicted 25% of all new-onset CVD. In the absence of diabetes, the metabolic syndrome generally did not raise 10-year risk for CHD to 20%; this is the threshold for ATP III's CHD risk equivalent. Ten-year risk in men with metabolic syndrome generally ranged from 10% to 20%. Framingham women with metabolic syndrome had relatively few CHD events during the course of the 8-year follow-up; this was due in part to the high proportion of women who were under 50

years of age. Although the metabolic syndrome in these women appeared to be accompanied by higher risk for CVD/CHD, the confidence interval was wide, and differences between those with and without metabolic syndrome were not statistically significant.

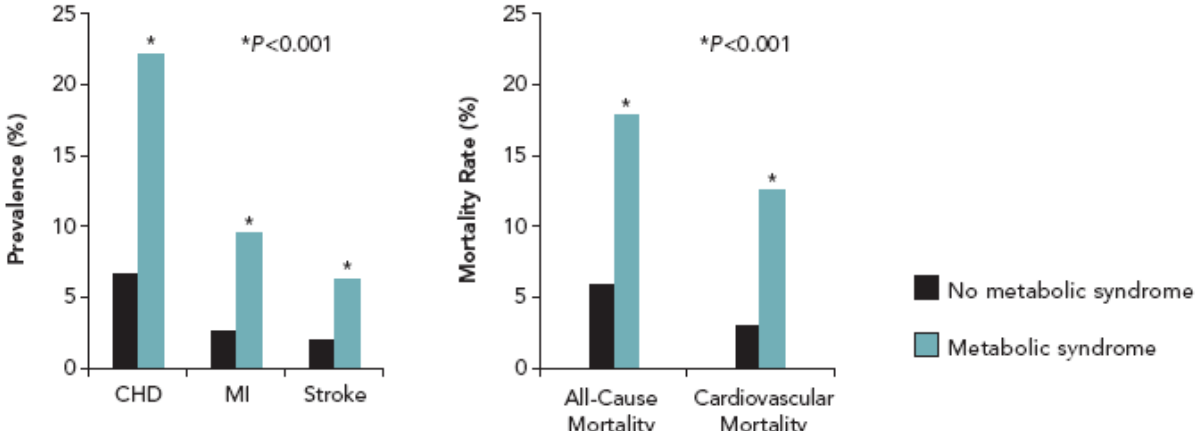
Metabolic Syndrome as a Predictor of Diabetes

When the risk for new-onset diabetes was examined for the Framingham cohort, in both men and women, the presence of metabolic syndrome was highly predictive of new-onset diabetes[16]. Almost half of the population-attributable risk for diabetes could be explained by the presence of ATP III metabolic syndrome.

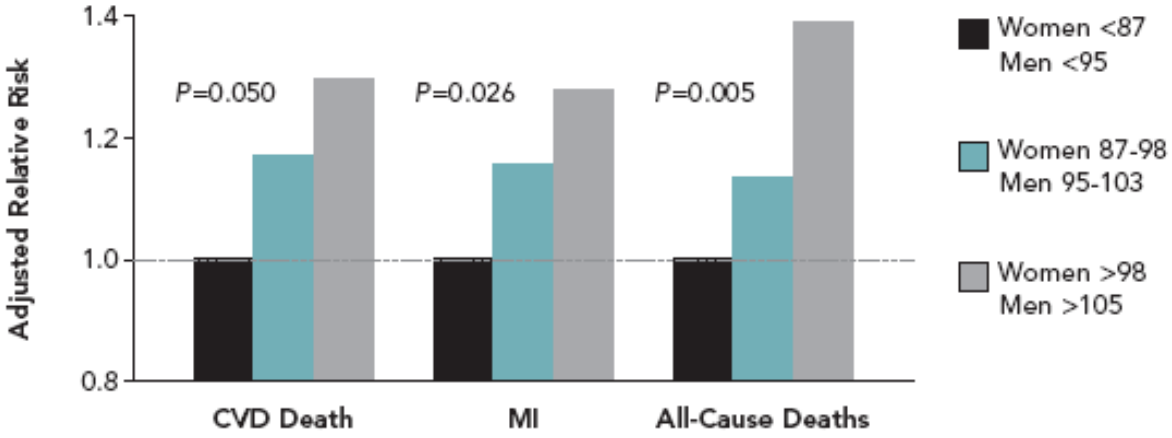
Diabetes as a Predictor of CVD

Framingham data showed that most men with diabetes had a 10-year risk for CHD > 20%; in contrast, women rarely exceeded the 20% level. Oxford investigators therefore have developed a risk engine (available on the World Wide Web) based on the large UK Prospective Diabetes Study (UKPDS) database, which had 500 hard CHD events[5,16]. It differs from the Framingham algorithm in that it includes a measure of glycemia and duration of diabetes. Surveys of other diabetic populations by UKPDS investigators found that Framingham equations considerably underestimate risk for CHD and stroke, whereas the UKPDS Risk Engine provides a more robust estimate.

Metabolic Syndrome Associated With Increased CV Morbidity and Mortality[16,18]



Waist Circumference and cardiovascular events[16,18]



ATP III Guidelines for the Treatment of Patients with Metabolic Syndrome[11,17]

Targeted area	*Goal*
Treat LDL cholesterol first.	
CHD and CHD risk equivalent (10-year risk for CHD >20 percent)	<100 mg per dL (<2.60 mmol per L)
At least two risk factors and 10-year risk ≤20 percent	<130 mg per dL (<3.35 mmol per L)
Institute weight control.	–10 percent from baseline
Institute physical activity.	30 to 40 minutes per day, three to five days per week
Monitor treatment of hypertension.	<130/85 mm Hg
Treat elevated triglyceride levels and low HDL cholesterol levels.	
Goal of non-HDL cholesterol for patients with triglyceride levels of ≥200 mg per dL (≥5.20 mmol per L) and ≤499 mg per dL (≤12.90 mmol per L)	High CHD risk: <130 mg per dL Intermediate CHD risk: <160 mg per dL (4.15 mmol per L) Low CHD risk: <190 mg per dL (4.90 mmol per L)

Pharmacotherapeutic strategies targeting the Metabolic syndrome

ACE-inhibitors (ACE-I) and AT1-receptor antagonists (ARBs)

Insulin resistance is known to activate the RAS [DeFronzo and Ferrannini, 1991]. Angiotensin II as the main effector of the RAS not only increases the vascular resistance, but also increases hepatic glucose production and decreases insulin sensitivity. Therefore it is obvious that pharmacological inhibition of the RAS does not only exert antihypertensive effects but also targets insulin resistance and improves the glucose metabolism. The question whether an ACE-I or an angiotensin receptor blocker (ARB) should be used remains controversial. There is consensus that ARBs may be used when ACE-I are not tolerated and have similar beneficial effects in preventing diabetes [Barnett et al. 2004]. In contrast to ACE-I, ARBs directly block the AT1-receptor and hence also the action of angiotensin II produced via non-ACE-dependent pathways[20].

However, there are two additional pharmacological arguments supporting the use of an ARB. ARB results in significant increases of the pleiotropic and vasodilatory angiotensin II – metabolite angiotensin 1-7 [Ang-(1-7)] [Schindler et al. 2007], which might improve the antihypertensive effects, whereas treatment with an ACE-I results in increases of bradykinin-levels, which do not seem to have beneficial vascular effects [Schindler et al. 2007]. These observations suggest telmisartan as a promising cardiometabolic ARB, which targets the RAS via selective AT1-receptor antagonism and insulin resistance via binding to the intracellular PPAR γ -complex, which has been shown to improve insulin resistance.

Endothelin (ET)-Antagonists

Cardillo et al. have shown that selective ET-A-blockade in the forearm resulted in a significant increase in forearm blood flow (FBF) in patients with type II diabetes but not in healthy individuals, whereas nonselective ET-A/ET-B blockade in diabetics did not significantly modify the effects of ET-A antagonism [Cardillo et al. 2002a][20]. Considering a potential role for endothelin in hypertension and in insulin resistant states especially with respect to the ability of angiotensin II to stimulate ET production, endothelin-antagonists might be an additional therapeutic option for treating the MetS, maybe in combination with a drug inhibiting the RAS.

Calcium channel blockers (CCBs)

CCBs appear to have beneficial effects with respect to maintenance of renal blood flow and glomerular filtration rate [Sowers, 1997b].

PPAR-receptor complex stimulation as therapeutical target

PPARs are ligand-activated transcription factors and belong to the nuclear receptor super family, which also includes the steroid and thyroid hormone receptors. The PPAR family consists of three members, α, γ and β/δ, which share 60 to 80% homology in their ligand- and DNA-binding domains. PPARα can be activated by certain polyunsaturated fatty acids, by oxidized phospholipids and by lipoprotein lipolytic products [Ziouzenkova et al. 2003]. Fibrates and gemfibrocil are synthetic ligands [Formann et al. 1997], which are used as drugs for the treatment of hypertriglyceridemia [Yuan et al. 2007]. PPARα regulates genes that are involved in lipid and lipoprotein metabolism. PPARγ is activated by prostaglandin-derivatives and forms of oxidized linoleic acid as natural ligands. Synthetic ligands currently available for drug treatment include the thiazolidinediones (glitazones)[19] rosiglitazone and pioglitazone. **Glitazones** functioning as PPARγ –activators play an important role in glucose homeostasis and reduce peripheral insulin resistance of patients with type 2 diabetes [Saltiel and Olefsky, 1996][19,20]. PPARα/γ dual agonists such as muraglitazar or tesaglitazar have been developed to target both PPARα and PPARγ simultaneously in order to produce synergistic antidiabetic and cardioprotective effects[24]. Dual agonists have been demonstrated to reduce triglycerides, raise cardioprotective HDL levels and consequently improve insulin sensitivity [Kendall et al. 2006].

Statins

The pleiotropic effects of statins improves cardiovascular outcomes beyond their

ability to improve atherogenic lipid profiles [McFarlane et al. 2002]. Modulation of endothelial function, plaque stabilization, attenuated atherogenesis, anti-inflammatory and antithrombotic effects might support the cardiometabolic risk reduction in patients with the Metabolic Syndrome.

CETP-inhibition with torcetrapib

CETP-inhibition has been regarded as a promising therapeutic concept to reduce the total cardiovascular risk. However, the CETP-inhibitor drug torcetrapib, which was designed to selectively increase HDL-levels by blocking CETP showed that, although the drug raises HDL as expected, it doesn't halt the progression of atherosclerosis[21].

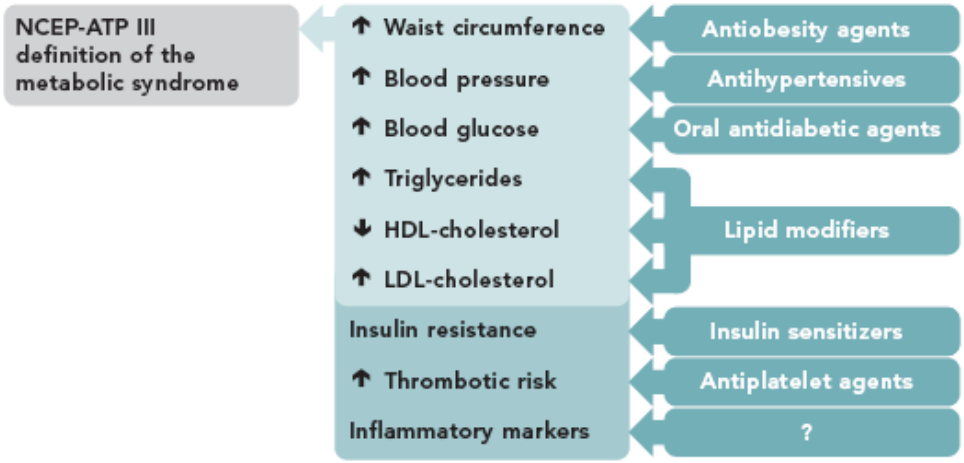
Sibutramine, orlistat and rimonabant

Sibutramine, a centrally acting appetite suppressant, and orlistat, a locally acting inhibitor of nutrient absorption, pharmacologically target obesity as a component of the MetS. Sibutramine acts on the CNS by inhibiting the reuptake of norepinephrine and serotonin and thereby amplifies satiety signals that induce a sensation of fullness[24]. **Orlistat** is a drug that reduces fat absorption by binding to pancreatic lipases, which partially inhibits the hydrolysis of triglycerides into absorbable free fatty acids and monoacylglycerols [Yanovski et al. 2002].

Rimonabant is a selective cannabinoid-1 receptor blocker. The endocannabinoid system plays a role in the central and peripheral regulation of body weight and energy balance [Van Gaal et al. 2005]. Three Rimonabant In Obesity/Overweight (RIO)-trials demonstrated that the drug reduces weight and waist circumference and improves

numerous cardiovascular and metabolic risk factors. In all trials, rimonabant was associated with an increased HDL cholesterol and decreased waist circumference and triglycerides[25].

Current Therapies Often Address Individual Risk Factors Instead of a Root Cause[22,23]



AIM AND OBJECTIVES OF THE STUDY

- To evaluate the effects of the metabolic syndrome on echocardiographically determined left ventricular structure and function.
- To evaluate the systolic and diastolic dysfunction in patients with the metabolic syndrome.

MATERIALS AND METHODS

Clinical setting

The people attending diabetic outpatients clinic with impaired fasting glucose and impaired glucose tolerance for regular follow up.

Collaborating departments

Department of Diabetology,

Madurai Medical College,

Madurai.

Department of Biochemistry,

Madurai Medical College,

Madurai.

Design of study : case control study

Period of study: 1 year

Sample size: 100 cases and 25 controls

Study population

Cases

Among the people attending diabetic outpatients clinic with impaired fasting glucose and impaired glucose tolerance for regular follow up, 100 people with waist circumference satisfying the criteria for the metabolic syndrome were selected.

Males – 50

Females – 50

Controls

Healthy attenders accompanying the follow up patients and diabetic patients, screened for plasma glucose and having normal waist circumference. The number of controls included in the study was 25.

Inclusion criteria

- Males and females who satisfy the criteria for the definition of the metabolic syndrome.
- They did not have established coronary artery disease, as evidenced by a negative Treadmill test.
- They had normal LV systolic function.

Exclusion criteria

- History or findings suggesting cardiovascular disease including heart failure symptoms, or systolic dysfunction, coronary artery disease, significant valvular heart disease, and/ or hypertrophic cardiomyopathy.
- Pregnancy and lactating mothers.
- Those who had major systemic illness.

The metabolic syndrome was defined according to IDF criteria and is as follows :

Central obesity (defined as waist circumference ≥90 cm for men and ≥80 cm for women.

Plus any 2 of the following 4 factors:

- Raised triglyceride level ≥150 mg/dL, or specific treatment for this lipid abnormality
- Reduced HDL-C <40 mg/dL in males, <50 mg/dL in females, or specific treatment for this lipid abnormality
- Raised BP: systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose ≥100 mg/dL, or previously diagnosed type 2 diabetes.

Study method

All the study subjects and controls underwent a complete cardiovascular evaluation after an 8 hours fast including

- History and physical examination
- Heart rate and blood pressure (obtained after 10 minutes of rest in the sitting position, expressed as the average of 3 consecutive measurements in each arm)
- Fasting and postprandial plasma glucose.
- Fasting lipid profile
- A comprehensive 2D and Doppler echocardiogram, along with 3D strain echocardiographic evaluation.

We had obtained permission from ethical committee for the study.

Informed consent was obtained from each patient, prior to study enrollment.

After this initial evaluation clinically and biochemically, cases were selected using

the International Diabetes Federation criteria for the diagnosis of metabolic syndrome. 25 controls were enrolled, who had normal waist circumference and do not meet other criteria. In the cases group, 10% were in the age group of <40 years, 76% were between 40 and 60 years, and 14% were >60 years.

The frequency of various components of metabolic syndrome changed from 3 components in 14%, 4 components in 68%, to 5 components in 18%.

Then the prevalence of the various components of the metabolic syndrome were analysed. 100% of the cases met the criteria for waist circumference and impaired fasting glucose/ impaired glucose tolerance. 80% of the cases had elevated blood pressure, 74% had increased triglycerides level and 52% had decreased HDL levels.

Echocardiographic evaluation

The patients and controls underwent two dimensional, M-mode, and Doppler echocardiography according to a standardized protocol.

Echocardiography was performed using dedicated 3D echocardiographic system, Philips iE 33 with QLAB software and Aloka SSD 4000 Echocardiography Sysetm.

First left ventricular internal dimensions and wall thickness were measured using standard recommendations and ejection fraction was found using M-mode and Simpson method.

EF calculation from volume data obtained by Simpson method:

Stroke volume = End diastolic volume (EDV) – End systolic volume (ESV)

$$EF = \frac{EDV - ESV}{\text{————}} \times 100\%$$

EDV

Left atrial diameter was measured in parasternal long axis view.

Relative wall thickness was measured as follows:

$$RWT = \frac{\text{Posterior wall thickness + IVS thickness}}{\text{LV interior dimension}}$$

LV mass was calculated using the formula

$LV\ mass = (IVS+LVID+PW)^3 - LVID^3 \times 1.05\ g/cm^3$

LV mass was indexed to body surface area to get LV mass index.

Left ventricular hypertrophy was diagnosed when the LV mass index was $\geq 131 g/m^2$ in men and $\geq 100 g/m^2$ in women. Increased relative wall thickness+ normal LV mass is concentric remodeling. Increased relative wall thickness + increased LV mass is concentric hypertrophy. Normal relative wall thickness + increased LV mass is eccentric hypertrophy.

In all the patients and controls, diastolic dysfunction was assessed by pulsed-wave Doppler examination of mitral flow (before and during Valsalva maneuver) and pulmonary venous inflow, as well as by Doppler tissue imaging of the mitral annulus. Diastolic dysfunction was graded on a 4-point ordinal scale: normal; mild diastolic dysfunction, defined as abnormal relaxation without increased LV end-diastolic filling pressure (peak early (E) to peak late [atrial] [A] diastolic filling velocity ratio <1); moderate or "pseudonormal" diastolic dysfunction, defined as abnormal relaxation with increased LV end-diastolic filling pressure (E/A ratio of 1 to 2, deceleration time >140

ms, and 2 other Doppler indices of elevated LV end-diastolic filling pressure); or severe diastolic dysfunction, defined as advanced reduction in compliance with restrictive filling (E/ A ratio >2, deceleration time <140 ms, and Doppler indices of elevated LV end-diastolic filling pressure). For patients in atrial fibrillation, diastolic function was classified as indeterminate unless restrictive physiologic factors (E/A ratio >1.5, deceleration time <140 ms) were present.

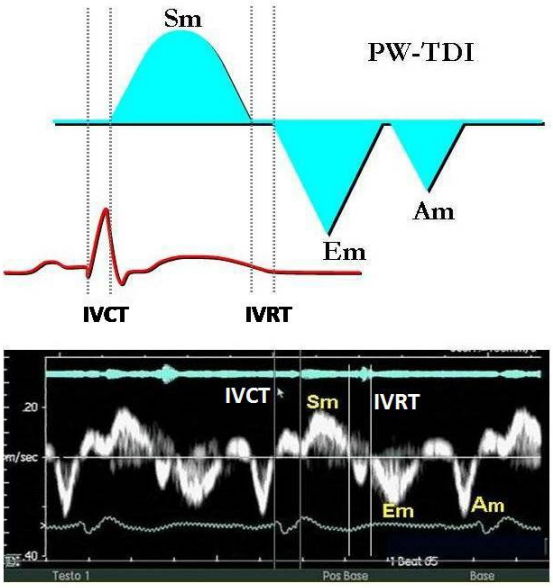
The pulse wave doppler study of right upper pulmonary venous flow was done. There were systolic (S), diastolic (D), and atrial reversal (Ar) waves. In normal and grade 1 diastolic dysfunction, S ≥ D and Ar duration < A duration. In Grade II, grade III and Grade IV diastolic dysfunction, S<D and Ar duration > A duration+ 30ms.

Then Tissue Doppler imaging study with sample volume on the septal side of the mitral annulus was done and the S', E', and A' waves were obtained. In normal and Grade I diastolic dysfunction, E/E' was <10. In Grade II, Grade III, and Grade IV diastolic dysfunction, E/E' was ≥ 10.

From the tissue Doppler image, the values of isovolumic contraction time, ejection time and isovolumic relaxation time were obtained. The myocardial performance index or Tei index was obtained using the formula,

$$MPI = IVCT + IVRT / ET.$$

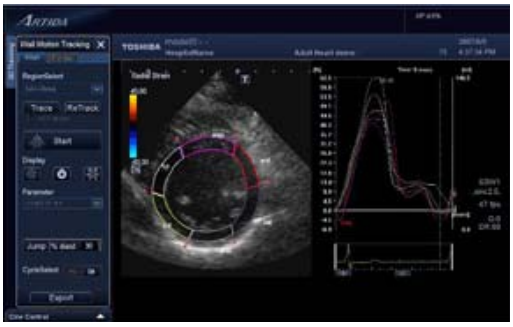
MPI values were elevated in patients who had either systolic or diastolic dysfunction.

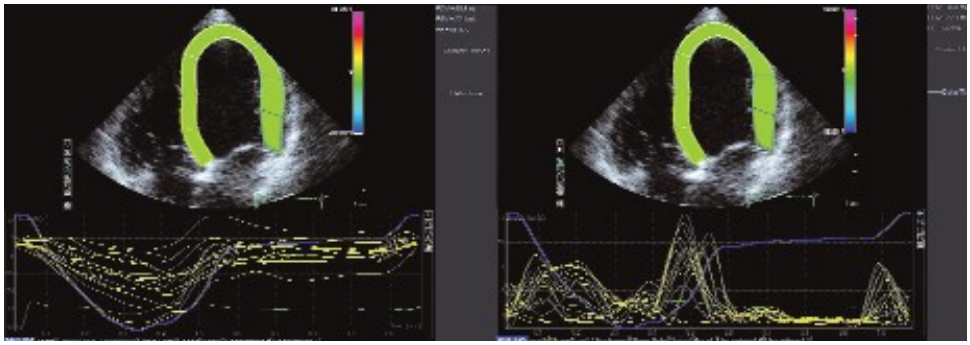


Normal PW-TDI spectral curve: note the immediate representation of the mechanical events in the various phases of the cardiac cycle.

Then all the patients underwent strain imaging with speckle tracking echocardiography and parametric images were obtained. From these images, peak systolic strain and early diastolic strain and strain rate were obtained.

End diastole **End systole**





The longitudinal strain, radial strain, and radial strain rate were obtained for 50 cases and 10 controls were obtained. The strain values and strain rate values were analysed.

STATISTICAL ANALYSIS

The information collected regarding all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using Epidemiological information package (EPI 2002). Using this software, frequencies, percentages, mean, standard deviation, α 2 and 'p' values are calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATIONS

The observations in the study related to the characteristics of the cases and controls, their biochemical profile and echocardiographic abnormalities were analysed.

In the study population of 100 cases, 50 were males and 50 were females.

The age distribution of the cases and controls is shown in table 1

Table 1

Distribution of cases and controls according to age

Age group	Cases (%)	Controls (%)
< 40 years	10 (10%)	3 (12%)
40 – 60 years	76 (76%)	19 (76%)
> 60 years	14 (14%)	3 (12%)

In Table 2, the frequency of various components of metabolic syndrome in the

study cases are shown.

Table 2

Frequency of the components of metabolic syndrome

Number of components	Number of patients (%)
Three	14 (14%)
Four	68 (68%)
Five	18 (18%)

In table 3, the prevalence of various components of metabolic syndrome are listed. Since we followed IDF criteria for metabolic syndrome, 100% of patients satisfied the waist circumference criteria. 100% of patients had IFG / IGT.

Table 3

Prevalence of components of metabolic syndrome

No.	Components	Percentage of prevalence
1.	Waist circumference	

	- In males > 90 cm - In females > 80 cm	100% 100%
2.	Blood pressure ≥ 130/85 mm Hg	80%
3.	Impaired fasting glucose / Impaired glucose tolerance	100%
4.	Triglycerides ≥ 150 mg %	74%
5.	High density lipoprotein - In males < 40 mg% - In females < 50 mg%	52% 20% 32%

Table 4

Characteristics of the study cases and controls

No.	Characteristics	Cases	Controls
1.	Mean age (years)	51 ± 11	48 ± 10
2.	BMI (Kg/ m^2)	28 ± 3	23 ± 2
3.	Waist circumference (cm)	94 ± 6	82 ± 5
4.	Systolic blood pressure (mm Hg)	148 ± 7	136 ± 6
5.	Diastolic blood pressure (mm Hg)	92 ± 4	81 ± 4
6.	Fasting plasma glucose (mg%)	114 ± 5	92 ± 8
7.	Postprandial plasma glucose (mg %)	156 ± 10	104 ± 10
8.	Total cholesterol (mg%)	200 ± 18	190 ± 12
9.	LDL cholesterol (mg%)	126 ± 30	120 ± 14
10.	HDL cholesterol (mg%)	43 ± 9	46 ± 10
11.	Triglycerides	172 ± 20	148 ± 10
12.	VLDL cholesterol (mg%)	40 ± 6	36 ± 5

Table 5

Echocardiographic abnormalities

No.	Parameters	In cases	In controls	P value
1.	LVID (diastole) (mm)	47 ± 5	45 ± 4	
	LVID (systole) (mm)	32 ± 5	30 ± 4	
2.	Ejection fraction	59 ± 4	60 ± 5	
3.	LV mass (gm)	180 ± 40	158 ± 22	
4.	LV mass index (gm/m^2)	105 ± 22	92 ± 16	<0.0001
5.	Relative wall thickness	0.45 ± 0.3	0.39 ± 0.3	<0.0001
6.	Left atrial diameter (cm)	3.8 ± 0.4	3.4 ± 0.4	0.002
7.	PWD – mitral inflow			
	- E wave (cm/s)	74 ± 16	70 ± 10	
	- A wave (cm/s)	64 ± 14	48 ± 12	<0.0001
	- E/A ratio	1.2 ± 0.5	1.5 ± 0.4	<0.0001
	- Deceleration time (ms)	188 ± 20	160 ± 16	<0.0001
	- IVRT (ms)	88 ± 10	70 ± 8	0.002
8.	PWD – pulmonary venous flow			
	- S wave (cm/s)	52 ± 8	54 ± 8	
	- D wave (cm/s)	47 ± 8	44 ± 6	
	- Ar wave (cm/s)	31 ± 5	30 ±7	
9.	Tissue Doppler imaging			
	- S’ (cm/s)	8 ± 2	8 ± 2	
	- E’ (cm/s)	8 ± 2	10 ± 2	<0.0001
	- A’ (cm/s)	9 ± 3	8 ± 3	
10.	E/E’	10 ± 2	8 ± 1	

1.	IVCT (ms)	37 ± 5	35 ± 5	
12.	IVRT (ms)	86 ± 10	70 ± 10	0.002
13.	Ejection time (ms)	262 ± 10	290 ± 30	
14.	Myocardial performance index	0.45 ± 0.08	0.35 ± 0.04	<0.0001

In table 6, the number of patients having concentric remodeling, concentric hypertrophy, and eccentric hypertrophy are shown.

Table 6
Distribution of changes in left ventricular structure

No.	Change in LV structure	Percentage of cases (%)
1.	Concentric remodelling	50%
2.	Concentric hypertrophy	12%
3.	Eccentric hypertrophy	---

In table 7, the percentage of patients in each class of diastolic dysfunction are shown.

Table 7

Percentage of cases and controls having diastolic dysfunction

Grading of diastolic dysfunction	In cases	In controls
No diastolic dysfunction	46 %	
Grade I diastolic dysfunction	40 %	21 %
Grade II diastolic dysfunction	14 %	---
Grade III & IV diastolic dysfunction	----	---

In table 8, we have correlated patients having diastolic dysfunction in metabolic syndrome with myocardial performance index and there is a direct correlation between increasing grades of diastolic dysfunction and elevated MPI.

Table 8

Correlation between grading of diastolic dysfunction and MPI

No.	Patients with diastolic dysfunction	MPI	P-value
1.	No diastolic dysfunction	0.36 ± 0.03	
2.	Grade I diastolic dysfunction	0.44 ± 0.04	<0.0001
3.	Grade II diastolic dysfunction	0.50 ± 0.04	<0.0001

Strain imaging by speckle tracking echocardiography

Table 9 shows the mean strain imaging values of various segments in patients with metabolic syndrome, compared with controls.

Table 9

Peak systolic strain

No.	Longitudinal strain in segments	In cases (%)	In controls (%)
1.	Basal septal	9 ± 2	15 ± 2
2.	Mid septal	7 ± 1	18 ± 3
3.	Apical septal	14 ± 3	14 ± 2
4.	Apex	12 ± 3	14 ± 2
5.	Apicolateral	15 ± 3	15 ± 4
6.	Mid lateral	21 ± 3	22 ± 4
7.	Basal lateral	25 ± 3	26 ± 4
	Radial strain in segments		
1.	Basal septal	20 ± 5	26 ± 5
2.	Mid septal	22 ± 4	28 ± 3
3.	Apical septal	28 ± 4	29 ± 6
4.	Apex	22 ± 4	27 ± 4
5.	Apicolateral	26 ± 3	27 ± 5
6.	Midlateral	30 ± 5	32 ± 6
7.	Basal lateral	29 ± 4	33 ± 5
	Radial strain rate in segments	Cases (s-1)	
1.	Basal septal	1.4 ± 0.2	2.0 ± 0.3
2.	Midseptal	1.5 ± 0.3	2.2 ± 0.4
3.	Apical septal	1.5 ± 0.2	1.9 ± 0.3
4.	Apex	1.5 ± 0.3	1.5 ± 0.3
5.	Apicolateral	1.7 ± 0.4	2.1 ± 0.2
6.	Midlateral	1.8 ± 0.4	1.9 ± 0.2
7.	Basal lateral	1.9 ± 0.2	2.0 ± 0.3

Early diastolic strain

	Longitudinal strain	Cases (%)	Controls (%)
1.	Basal septal	9 ± 2	14 ± 2
2.	Mid septal	8 ± 3	15 ± 2
3.	Apical septal	16 ± 3	16 ± 2
4.	Apex	15 ± 2	15 ± 3
5.	Apical lateral	16 ± 3	18 ± 2
6.	Mid lateral	22 ± 5	27 ± 5
7.	Basal lateral	28 ± 4	28 ± 3
	Radial strain in segments		
1.	Basal septal	20 ± 4	28 ± 4
2.	Mid septal	26 ± 4	28 ± 5
3.	Apical septal	25 ± 8	27 ± 5
4.	Apex	26 ± 4	25 ± 6
5.	Apical lateral	28 ± 3	27 ± 5
6.	Mid lateral	32 ± 5	32 ± 6
7.	Basal lateral	38 ± 5	39 ± 5
	Radial strain rate in segments		
1.	Basal septal	1.5 ± 0.3	1.8 ± 0.2
2.	Mid septal	1.6 ± 0.4	2.0 ± 0.3
3.	Apical septal	1.6 ± 0.2	1.9 ± 0.2
4.	Apex	1.4 ± 0.2	1.5 ± 0.2
5.	Apical lateral	1.6 ± 0.2	2.0 ± 0.3
6.	Mid lateral	1.5 ± 0.3	2.1 ± 0.4
7.	Basal lateral	2.2 ± 0.3	2.5 ± 0.3

LIMITATIONS OF THE STUDY

In spite of meticulous conduct of the study, we have limitations in our study. Our Philips iE 33 echocardiography system is using Q LAB software. In this, we were not able to track the cardiac borders accurately in short axis. So, our values related to Radial strain differ while comparing with certain references.

CONCLUSION

The following conclusion was derived from this study.

1. The prevalence of Diastolic dysfunction is relatively high in patients with metabolic syndrome when compared to controls.
2. There is a significant change in LV structural characteristics in patients with metabolic syndrome when compared to controls. The parameters like LV mass, LV mass index, and relative wall thickness were significantly increased in patients with metabolic syndrome. Concentric remodeling was more common than concentric hypertrophy and eccentric hypertrophy in patients with metabolic syndrome
3. With the Pulse Doppler echocardiographic evaluation of mitral inflow, pulmonary venous flow, and tissue doppler imaging at mitral annulus, and applying the criteria for diastolic dysfunction, the prevalence of diastolic dysfunction is nearly 54% in patients with metabolic syndrome (Grade I diastolic dysfunction- 40% and Grade II diastolic dysfunction – 14%) when it is 21% in the controls.
4. Impaired relaxation (Grade I diastolic dysfunction) is more prevalent among patients with metabolic syndrome and signified subclinical LV diastolic dysfunction with masked cardiovascular disease.
5. Left Ventricular Myocardial Performance Index measured by Tissue Doppler Imaging, is having good correlation with the prevalence and degree of diastolic

dysfunction.

6. Finally, strain imaging in patients with metabolic syndrome with normal ejection fraction shows subclinical LV systolic dysfunction in addition to diastolic dysfunction, as evidenced by a decreased peak systolic strain.

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PROFORMA

ECHOCARDIOGRAPHIC ABNORMALITIES IN THE METABOLIC SYNDROME

Name of the patient : Age : Sex:

CD no : Address :

Clinical diagnosis :

Brief history :

General examination :

Build and nourishment

Height

Weight

Waist circumference

Hip measurement

Waist hip ratio

Pulse :

Blood pressure :

Cardiovascular system examination :

Respiratory system examination :

Abdomen :

CNS examination:

Investigations :

Urine - Albumin

- Sugar

- Deposits

Blood - Hb

- ESR

Blood urea

Blood sugar - F

- PP

Serum creatinine

Fasting lipid profile

Total – C LDL – C HDL – C

TGL VLDL

ECG

Echocardiogram :

2 D and M mode echo :

LVID (d) LVID (s)

EF LV mass

LV mass index Relative wall thickness

Left atrial diameter RWMA

Doppler echo :

Mitral inflow : E

A

DT

E/A

Pulmonary venous flow – S

D

A

TDI - S' E'

A' IVCT

IVRT ET

MPI

3 D echo:

Strain echo findings: